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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,508	08/09/2005	Hiroyuki Aburatani	392.1001	4237

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EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,508	ABURATANI ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-8 and 15-18 are pending and are under examination.

2. Applicant's election without traverse of the invention of Group I, and the election with traverse of the species "an amino acid sequence of GPC3 consisting of the 1st amino acid to the 374th amino acid" and "blood", in the reply filed Feb. 21, 2007 is acknowledged. The traversal is on the ground(s) that searching the various species would not pose an undue search burden. This argument is not found persuasive because, while the searches would be overlapping they would not be coextensive and thus would pose an undue search burden. The requirement for restriction is proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1-8 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 15-18 are indefinite because claim 1 does not contain a positive process step that clearly relates back to the preamble. Amendment of the claims to clarify exactly what is intended by the claims is required.

Claim 3 is indefinite because it is not clear whether the N-terminal peptide of GPC3 that is being detected is a fragment consisting of the 1st amino acid to the 374th amino acid or is any fragment contained within the fragment consisting of the 1st amino acid to the 374th amino acid.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

A method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample (**claim 1**),

Wherein the soluble GPC3 protein is a N-terminal peptide of GPC3 (**claim 2**),

Wherein the soluble GPC3 protein is a N-terminal peptide of GPC3, wherein the N-terminal peptide of GPC3 is a peptide fragment contained in an amino acid sequence of GPC3 consisting of the 1st amino acid to the 374th amino acid (**claim 3**),

Wherein the test sample is a blood sample (**claim 4**),

Wherein the cancer is hepatic cancer (**claim 5**),

Comprising using an anti-GPC3 antibody (**claim 6**),

Comprising using an anti-GPC3 antibody, Comprising using an anti-GPC3 antibody immobilized on a carrier and an anti-GPC3 antibody labeled with a labeling substances (**claim 7**),

Comprising using an anti-GPC3 antibody, Comprising using an anti-GPC3 antibody immobilized on a carrier and an anti-GPC3 antibody labeled with a labeling substances, wherein the labeling substances are biotin (**claim 8**),

Wherein the soluble GPC3 protein is a N-terminal peptide of GPC3, wherein the N-terminal peptide of GPC3 is a peptide fragment contained in an amino acid sequence of GPC3 consisting of the 1st amino acid to the 374th amino acid, wherein the test sample is a blood sample (**claim 15**)

Wherein the soluble GPC3 protein is a N-terminal peptide of GPC3, wherein the N-terminal peptide of GPC3 is a peptide fragment contained in an amino acid sequence of GPC3 consisting of the 1st amino acid to the 374th amino acid, wherein the cancer is hepatic cancer (**claim 16**)

Wherein the test sample is a blood sample, wherein the cancer is hepatic cancer (**claim 17**),

Wherein the soluble GPC3 protein is a N-terminal peptide of GPC3, wherein the N-terminal peptide of GPC3 is a peptide fragment contained in an amino acid sequence of GPC3 consisting of the 1st amino acid to the 374th amino acid, comprising using an anti-GPC3 antibody (**claim 18**).

The specification teaches that cancers to be diagnosed according to the invention include but are not limited to hepatic cancer, pancreatic cancer, lung cancer, colon cancer, mammary cancer, prostate cancer, and lymphomas (page 5). The specification teaches that an expression analysis of GPC3 mRNA in human liver samples showed the expression of GPC3 mRNA was higher in hepatic cancer tissues than in normal liver tissues regardless of the differentiation stage of the hepatic cancer (page 34). The specification further teaches the preparation of monoclonal antibodies M6B1, M18D4, and M19B11 which recognized the N-terminal half of GPC-3 and monoclonal antibodies M3C11, M13B3, and M3B8 which recognize the C-terminal side of GPC-3 (page 42). The specification further teaches that secretory GPC3 was detected at high levels in the culture supernatant of the cell line HepG2 and in the sera of the mice to which HepG2 human hepatic cancer cells had been grafted using a combination of the M6B1 and M19B11antibodies, both of which recognize the N-terminal fragment, whereas the results obtained with antibodies recognizing the C-terminal fragment showed a GPC3 level below the detection limit (Table 1 and page 44). The specification further teaches that GPC3 is cleaved between the 358th and 359th amino acids (page 2). The specification further teaches that in mice grafted with the human hepatic cancer cell lines, the serum level of soluble GPC3 was 23 to 90 ng/ml.

The teaching of the specification cannot be reasonably extrapolated to enable the invention because one of skill in the art could not predict that the invention would function as contemplated given that the GPC3 protein was not demonstrated to be overexpressed in any in vivo cancer, particularly in any in vivo human cancer. In a first aspect, the teaching in the specification that the GPC3 mRNA is expressed at higher

levels in hepatic cancers than in normal liver tissues is not sufficient to establish that the GPC3 protein is expressed at higher levels in hepatic cancers than in normal liver tissues. In particular, the prior art is replete with examples in which expression levels of mRNA are not correlated with expression levels of the encoded protein. For example, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF-alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable, and Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and levels of S100 alpha protein. Further, Eriksson et al. (Diabetologia, 1992, vol. 35, pp. 143-147) teaches that no correlation is observed between levels of mRNA transcripts encoding the insulin-responsive glucose transporter and expression levels of the protein. Thus, observation of expression of mRNA does not appear to be predictive of concomitant expression of protein. In a second aspect, the teaching of the specification that the GPC3 soluble protein is detected in the supernatant of cultured cell lines or that soluble GPC3 protein is detected in the sera of mice that have been grafted with a human hepatic cancer cell line are not sufficient to establish that soluble GPC3 protein would be produced from hepatic cancers in vivo. In particular, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo, wherein these differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate and the fact that the culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Thus, given the art recognized lack of a predictable correlation between protein and RNA and expression, given the art recognized differences between cultured cells and cells in the in vivo environment, and given the lack of guidance on these issues in the specification such as by way of working examples, one of skill in the art could not predict that the invention would function as claimed in diagnosing cancer. Thus, practice of the invention would require undue experimentation.

7. If rejection of claims 1-8 and 15-18, under 35 U.S.C. 112, first paragraph, for lack of enablement, as stated in paragraph 6 above, is overcome, claims 1-8 and 15-18 would still be rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, because the specification, while being enabling for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, wherein the amount of soluble GPC3 protein in the test sample is at least 23 ng/ml, does not reasonably provide enablement for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample.

The claims are as set forth above.

The specification teaches as set forth above.

One of skill in the art could not reasonably extrapolate the teaching of the specification to enable the scope of the claims because the art teaches that levels of soluble GPC3 protein are found in the sera in conjunction with conditions other than cancer. In particular, Hippo et al. (2004, Cancer Research 64:2418-2423) teaches that serum levels of soluble GPC3 protein in patients with liver cirrhosis were 1.09 ± 0.74 ng/ml, a level that is higher than the level seen in healthy controls of 0.65 ± 0.74 ng/ml. Given the above, it is clear that one could not predictably distinguish cancer from normal controls or patients with liver cirrhosis in the absence of a cut-off point that would differentiate between the cancer and levels of GPC3 protein found in normal patients and patients with other diseases that present with soluble GPC3 protein. Thus,

one of skill in the art could not predict that the invention would function as claimed in diagnosing cancer wherein any level of soluble GPC3 protein is detected in sample. Thus, practice of the invention would require undue experimentation.

8. If rejection of claims 1-8 and 15-18, under 35 U.S.C. 112, first paragraph, for lack of enablement, as stated in paragraph 6 above, is overcome, claims 5 and 16-17 would still be rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, because the specification, while being enabling for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, does not reasonably provide enablement for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, wherein the cancer is a hepatic cancer.

The claims are as set forth above.

The specification teaches as set forth above.

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predict that the presence of a detectable level of GPC3 in a body fluid sample of a subject would allow for the diagnosis of hepatic cancer as it would not be possible to determine the type of cancer present. The specification teaches a correlation of detectectable soluble GPC3 expression with hepatocellular carcinoma. Further, the art teaches that the GPC3 protein was detected in sera from 40% of patients with melanoma, but not from healthy donors, that serum GPC3 was detected even in patients with stage 0, in situ melanoma, with a positive detection rate of serum GPC3 at melanoma stages 0, I, and II of 44.4%, 40.0%, 47.6% respectively) (Nakatsura et al., 2005, Biodrugs 19(2):71-77). Thus, the detection of soluble GPC3 in blood could indicate the presence of melanoma or hepatocellular carcinoma and merely the detection of GPC3 in sera would not allow one of skill in the art to diagnose the presence of a particular cancer. For the above reasons, it appears that undue experimentation would be required to practice the

claimed invention.

9. If rejection of claims 1-8 and 15-18, under 35 U.S.C. 112, first paragraph, for lack of enablement, as stated in paragraph 6 and 7 above, is overcome, claims 3 and 15-16 would still be rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, because the specification, while being enabling for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, wherein the soluble GPC3 protein is an N-terminal peptide of GPC3 consisting of the 1st amino acid to the 358th amino acid does not reasonably provide enablement for a method for diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, wherein the soluble GPC3 protein is a N-terminal peptide of GPC3 consisting of the 1st amino acid to the 374th amino acid.

The claims are as set forth above.

The specification teaches as set forth above.

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predict that the invention would function as claimed in diagnosing cancer, which comprises detecting a soluble GPC3 protein in a test sample, wherein the soluble GPC3 protein is a N-terminal peptide of GPC3 consisting of the 1st amino acid to the 374th amino acid. In particular, the specification teaches that GPC3 is cleaved between the 358th and 359th amino acids. Thus, one of skill in the art could not predict that the invention would function as claimed in detecting a soluble GPC3 protein in a test sample, wherein the soluble GPC3 protein is a N-terminal peptide of GPC3 consisting of the 1st amino acid to the 374th amino acid. Thus, practice of the invention would require undue experimentation.

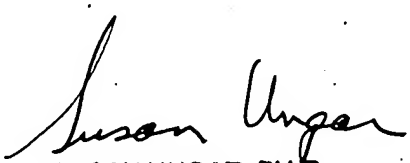
10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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PRIMARY EXAMINER

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